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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,481	01/20/2004	Nozer M. Mehta	P/546-280	2921

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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	PAPER NUMBER
1654	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,481	MEHTA ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-15,17-37,39-46,48-53,55,57-60 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-15,17-37,39-46,48-53,55,57-60 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 2, 2010 has been entered.

2. Claims 41, 42, 59, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claim 1 has been amended to recite that a physiologically active peptide agent that is not naturally amidated at its C-terminus has an amide group added at its C-terminus. Dependent claim 41 specifies that the physiologically active peptide agent is PTH 1-31NH_2. It is not clear if claim 41 specifies the physiologically active peptide agent which still needs to be amidated at its C terminus for purposes of the claimed invention; or if claim 41 in effect specifies that PTH 1-31 is the physiologically active peptide agent which is not naturally amidated at its C-terminus and that PTH 1-31NH_2 is this physiologically active peptide agent which has had an amide group added at its C-terminus. If the former interpretation is intended by Applicants, then the claim is indefinite because the C-terminal residue of PTH 1-31NH_2 is Val, which does not comprise any other possible amidation locations. If the latter interpretation is intended by Applicants, then the claims would read on oral pharmaceutical compositions comprising a known human parathyroid hormone analog, PTH 1-31NH_2. Similarly with respect to claim 42, it is not clear if the claim requires PTH 1-34NH_2 to be further amidated at its C-terminus, or if the NH_2 group in PTH 1-34NH_2 is the result of the amidation at the C-terminus recited in the claim. If the former interpretation is intended by

Applicants, then the claim is indefinite because the C-terminal residue of PTH 1-34NH_2 is Phe, which does not comprise any other possible amidation locations. If the latter interpretation is intended by Applicants, then the recitation "is amidated at its C-terminus where it is not naturally amidated" becomes superfluous. For reasons analogous to those set forth above with respect to claims 41 and 42, claims 59 and 60 are also indefinite.

3. The effective filing date of instant claims 1-3, 5-15, 17-37, 39-46, 48-53, 55, 57-60, and 63 is January 21, 2003, the filing date of provisional application 60/441,856. Instant claims 1-3, 5-15, 17-37, 39-46, 48-53, 55, 57-60, and 63 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the provisional application because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed subject matter.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1-3, 5-8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892). Stern et al teach oral administration of peptides such as insulin and parathyroid hormone using a carrier comprising a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating. See, e.g., column 6, line 1 - column 12, line 10, and claims 1-55. Stern et al do not teach peptides which are GLP-1 analogs which are amidated at their C-terminus, insulin analogs which are amidated at their C-terminus, or PTH analogs which are amidated at their C-terminus. Habener teaches GLP-1 analogs which can be C-terminally

amidated. See, e.g., column 4, lines 14-25, and claims 1 and 4. Mandic teaches insulin analogs in which the carboxy terminus of the B chain is amidated. The insulin analogs have enhanced stability to insulin-degrading enzyme. See, e.g., the Abstract and Figures 1-2. Barbier et al teach the human parathyroid hormone derivative hPTH(1-31)NH_2, and teach that the derivative can be administered orally. See, e.g., column 2, lines 26-44, and column 14, lines 59-62. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Mandic and Barbier et al in the oral administration compositions of Stern et al because the oral administration compositions of Stern et al have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Mandic, and Barbier et al, because oral administration is easier for the patient. Applicants' claims would have been prima facie obvious at the time the invention was made because applying Stern et al's known and generally applicable technique, i.e. of combining peptides with a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating so that the peptides can be administered orally, to the known and specific peptides of Habener, Mandic, and Barbier et al, with only the expected result that the known and specific peptides of Habener, Mandic, and Barbier et al, can be administered orally, is prima facie obvious. See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (S. Ct. 2007). With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to instant claims 6 and 49, each of the GLP-1 analogs of Habener, the insulin analogs of Mandic, and the hPTH

analogs of Barbier et al comprises Gln and/or Asn residues, and therefore comprises amino acids containing amidated side chains.

6. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892) as applied against claims 1-3, 5-8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). Habener, Mandic, and Barbier et al teach known and specific peptides which are amidated at their C-termini, but do not teach synthesizing these peptides by forming glycine-extended precursors and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the known and specific peptides of Habener, Mandic, and Barbier et al for use in the oral administration compositions of Stern et al '918 by synthesizing the peptides as glycine-extended precursors and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teach that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

7. Claims 1-3, 5-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892). The WO Patent Application '767 teaches oral

administration of peptides such as insulin, salmon calcitonin, parathyroid hormone, lhrf, and GLP-1 linked to a membrane translocator using a carrier comprising a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating. See, e.g., page 17, lines 13-22, page 18, lines 10-27, page 20, lines 11-29, and claims 1-57. [Note that the WO Patent Application '767 does not designate the US, and therefore is not available as prior art under 35 U.S.C. 102(e).] The WO Patent Application '767 does not teach peptides which are GLP-1 analogs which are amidated at their C-terminus, insulin analogs which are amidated at their C-terminus, or PTH analogs which are amidated at their C-terminus. Habener teaches GLP-1 analogs which can be C-terminally amidated. See, e.g., column 4, lines 14-25, and claims 1 and 4. Mandic teaches insulin analogs in which the carboxy terminus of the B chain is amidated. The insulin analogs have enhanced stability to insulin-degrading enzyme. See, e.g., the Abstract and Figures 1-2. Barbier et al teach the human parathyroid hormone derivative hPTH(1-31)NH_2, and teach that the derivative can be administered orally. See, e.g., column 2, lines 26-44, and column 14, lines 59-62. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Mandic and Barbier et al in the oral administration compositions of the WO Patent Application '767 because the oral administration compositions have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Mandic and Barbier et al because oral administration is easier for the patient. Applicants' claims would have been prima facie obvious at the time the invention was made because applying the WO Patent Application '767's known and generally applicable technique, i.e. of combining peptides with a pH-lowering agent, a protease inhibitor,

an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating so that the peptides can be administered orally, to the known and specific peptides of Habener, Mandic and Barbier et al, with only the expected result that the known and specific peptides of Habener, Mandic and Barbier et al can be administered orally, is prima facie obvious. See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (S. Ct. 2007). With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to instant claims 6 and 49, each of the GLP-1 analogs of Habener, the insulin analogs of Mandic, and the hPTH analogs of Barbier et al comprises Gln and/or Asn residues, and therefore comprises amino acids containing amidated side chains.

8. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892) as applied against claims 1-3, 5-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). Habener, Mandic and Barbier et al teach known and specific peptides which are amidated at their C-termini, but do not teach synthesizing these peptides by forming glycine-extended precursors and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the known and specific peptides of Habener, Mandic and Barbier et al for use in the oral administration compositions of the WO Patent

Application '767 by synthesizing the peptides as glycine-extended precursors and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teaches that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

9. Claims 1, 5, 6, 17-19, 40, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by the Neugebauer et al article (Biochemistry, Vol. 34, pages 8835-8842). The Neugebauer et al article teaches a composition comprising hPTH(1-31)NH_2 combined with palmitoyloleoyl-phosphatidylserine vesicles in phosphate-buffered solution. See, e.g., page 8836, column 1, second full paragraph, and column 2, second paragraph; page 8839, Figure 7 and paragraph bridging columns 1 and 2. The palmitoyloleoyl-phosphatidylserine present in the vesicles of the Neugebauer et al article corresponds to Applicants' absorption enhancer. This rejection assumes that hPTH(1-31)NH_2 corresponds to Applicants' physiologically active peptide agent which has been amidated at its C-terminus, and that Applicants' claims do not require further C-terminal amidation of hPTH(1-31)NH_2. (See also the above rejection under 35 U.S.C. 112, second paragraph, for discussion of this issue of claim interpretation.) Note that an intended use limitation, e.g., "orally delivered", does not impart patentability to product claims where the product is otherwise anticipated by the prior art. Because the Neugebauer et al article teaches the only components specified in Applicants' claims, i.e. hPTH(1-31) amidated at its C-terminus and a phospholipid, inherently the composition of the Neugebauer et al article will provide enhanced bioavailability of the amidated peptide when it is orally delivered to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the compositions

of the Neugebauer et al article and Applicants' claimed compositions to shift the burden to Applicants to provide evidence that the claimed compositions are unobviously different than those of the Neugebauer et al article. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to instant claim 6, hPTH(1-31)NH_2 comprises Gln and Asn residues at positions 6, 10, 16, and 29, and thus comprises amino acids containing amidated side chains. With respect to instant claim 40, hPTH(1-31) and hPTH(1-31)NH_2 are analogs of human parathyroid hormone.

10. Applicant's arguments filed December 2, 2010 have been fully considered but they are not persuasive.

Holst et al (U.S. Patent Application Publication 2003/0091507) is cited as art of interest for its teaching that GLP-1(1-36)NH_2 and GLP-1(7-36)NH_2 are naturally amidated at their C-termini. See paragraph [0020]. Accordingly, these two peptides do not satisfy current claim requirements for an active peptide which has an amide group added at its C-terminus and wherein the active peptide is not naturally amidated at its C-terminus. Neiss et al (U.S. Patent No. 4,804,742), already of record, shows that calcitonin is naturally amidated at its C-terminus. See column 1, lines 13-30. Accordingly, calcitonin also does not satisfy current claim requirements for an active peptide which has an amide group added at its C-terminus and wherein the active peptide is not naturally amidated at its C-terminus.

With respect to dependent claims 6 and 49, the examiner is interpreting these claims as requiring an amidated side chain in addition to the amidated C-terminus required by the independent claims. This interpretation appears necessary to the examiner so that the dependent

claims do not contradict the limitations which have been added to the independent claims. If the examiner's interpretation is incorrect, Applicants must inform the examiner in the response to this Office action.

The obviousness rejections based upon Stern et al (U.S. Patent No. 6,086,918) or the WO Patent Application 02/043767, in view of Habener (U.S. Patent No. 5,120,712), Mandic (U.S. Patent Application Publication 2003/0104981), or Barbier et al (U.S. Patent No. 6,110,892), are maintained for the reasons of record. Applicants provide arguments supporting a conclusion that the instant claims are novel and unobvious over Stern et al and over the WO Patent Application '767. However, because the obviousness rejections are based upon Stern et al or the WO Patent Application '767 in combination with three other references, the arguments are unconvincing. Applicants' arguments do not address the combinations of references which are actually applied in the rejections. Note that Habener and Barbier et al, both previously applied in earlier Office actions, teach physiologically active peptide agents which are not naturally C-terminally amidated and to which have been added an amide group at their C-termini. Mandic is a newly cited reference, and again teaches a physiologically active peptide agent which is not naturally C-terminally amidated but which has been modified by C-terminal amidation.

The examiner agrees that the obviousness rejections of claims 5 and 48 will stand or fall with the corresponding obviousness rejections of the independent claims.

The anticipation rejection over the Neugebauer et al article (Biochemistry, Vol. 34, pages 8835-8842) is maintained for the reasons of record. In their arguments in favor of patentability over the Neugebauer et al article, Applicants repeat the limitations set forth in the rejected

claims, but do not identify with any particularity which of these limitations are not taught by the Neugebauer et al article.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/
Primary Examiner, Art Unit 1654

JRussel
January 27, 2011